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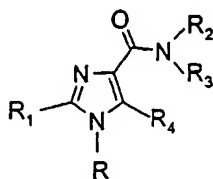
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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

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(54) Title: 1H-IMIDAZOLE DERIVATIVES HAVING CB₁ AGONISTIC, CB₁ PARTIAL AGONISTIC OR CB₁- ANTAGONIS-
TIC ACTIVITY



(I)

(57) Abstract: AbstractThe present invention relates to a group of novel 1H-imidazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component. These 1H-imidazole derivatives are potent cannabinoid-CB₁ receptor agonists, partial agonists or antagonists, useful for the treatment of psychiatric and neurological disorders, as well as and other diseases involving cannabinoid neurotransmission. The compounds have the general formula (I) wherein R and R₁-R₄ have the meanings given in the specification.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10434

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4164 C07D233/90 C07C257/18 C07D401/04 C07D403/04
C07D405/12 C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, vol. 133, no. 18, 30 October 2000 (2000-10-30) Columbus, Ohio, US; abstract no. 252124, LI, ZHI FANG ET AL: "Facile synthesis of amidines via intermolecular reductive coupling of nitriles with azobenzene promoted by samarium diiodide" XP002186058 see compound wherein R is 2,4-diClPh abstract & CHIN. CHEM. LETT. (2000), 11(6), 495-498, -/-	6,8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

4 December 2002

Date of mailing of the international search report

11/12/2002

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INTERNATIONAL SEARCH REPORT

National Application No

PCT/EP 02/10434

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TAISEI UEDA ET AL: "A novel ring transformation of 5-Acylaminouracils" TETRAHEDRON LETTERS, vol. 29, no. 36, 1988, pages 4607-4610, XP001038533 see Compound 3e	1
A	NORIAKI KUDO ET AL: "Synthesis and Herbicidal activity of 1,5-Diarylpyrazole derivatives" CHEM PHARM BULL, vol. 47, no. 6, 1999, pages 857-868, XP001026111 cited in the application	1
Y	see compounds 7,8,29a,29b	7
A	KHANNA I K ET AL: "1,2-DIARYLIMIDAZOLES AS POTENT, CYCLOOXYGENASE-2 SELECTIVE, AND ORALLY ACTIVE ANTIINFLAMMATORY AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 40, 1997, pages 1634-1647, XP000941303 ISSN: 0022-2623 cited in the application see table 7	1-10
Y	ISH KHANNA ET AL: "Selective Cyclooxygenase 2-Inhibitors" JOURNAL OF MEDICINAL CHEMISTRY, vol. 43, no. 16, 2000, pages 3168-3185, XP001026112 cited in the application See Scheme 9	4-8
Y	PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, August 1999 (1999-08), pages 635-664, XP000923352 ISSN: 0929-8673 see compounds on page 641 and pages 657-659	1-10
Y	US 5 616 601 A (KHANNA ISH ET AL) 1 April 1997 (1997-04-01) see especially formula 4, column 22	7
A	WO 00 63204 A (NOVARTIS ERFINDE VERWALT GMBH ;NOVARTIS AG (CH); REVESZ LASZLO (CH)) 26 October 2000 (2000-10-26) the whole document	1-10

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10434

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 46209 A (SANOFI SYNTHELABO ; BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN) 10 August 2000 (2000-08-10) the whole document	1-10
Y	THOMAS ET AL: "Comparative receptor binding analyses of cannabinoid agonists and antagonists" J PHARMACOL. EXP THER, vol. 285, no. 1, 1998, pages 285-292, XP000942485 see whole document	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/10434

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3, 9, 10
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3,9,10

Present claims 1-3,9,10 relate to a compound or use defined by reference to a desirable characteristic or property, namely that it be a prodrug of the formula I compounds.

The claims cover all compounds and uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds and uses. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula I and their use, and not their prodrugs.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/10434

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5616601	A	01-04-1997	AT 224374 T 15-10-2002
			AU 3202595 A 22-02-1996
			CA 2195845 A1 08-02-1996
			DE 69528273 D1 24-10-2002
			EP 0772600 A1 14-05-1997
			JP 10503211 T 24-03-1998
			WO 9603388 A1 08-02-1996
WO 0063204	A	26-10-2000	AU 4295300 A 02-11-2000
			BR 0010598 A 05-02-2002
			CN 1378544 T 06-11-2002
			CZ 20013696 A3 13-02-2002
			WO 0063204 A2 26-10-2000
			EP 1224180 A2 24-07-2002
			NO 20014987 A 14-12-2001
			SK 14562001 A3 05-03-2002
			TR 200102967 T2 21-01-2002
			US 2002049220 A1 25-04-2002
WO 0046209	A	10-08-2000	FR 2789078 A1 04-08-2000
			FR 2789079 A1 04-08-2000
			AU 2298900 A 25-08-2000
			BG 105749 A 28-02-2002
			BR 0007895 A 30-10-2001
			CN 1346349 T 24-04-2002
			CZ 20012697 A3 17-10-2001
			EE 200100399 A 15-10-2002
			EP 1150961 A1 07-11-2001
			WO 0046209 A1 10-08-2000
			HR 20010564 A1 31-08-2002
			JP 2002536366 T 29-10-2002
			NO 20013736 A 28-09-2001
			NZ 512886 A 25-10-2002
			PL 350030 A1 21-10-2002
			SK 10872001 A3 03-12-2001
			TR 200102054 T2 21-05-2002
			US 6432984 B1 13-08-2002

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